

# The Nanomedicine Revolution

## Part 2: Current and Future Clinical Applications

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This is the second in a series of three articles about nanomedicine. Part 1, in the September issue of *P&T*, focused on emerging concepts in nanomedicine. Part 3 will address the regulatory and safety challenges associated with nanomedicines.

### Introduction

Nanomedicine is a rapidly growing area of medical research that is focused on developing nanoparticles (NPs) for prophylactic, diagnostic, and therapeutic applications.<sup>1</sup> The unique properties of nanomedicines offer potential solutions for many of the current challenges in treating cancer, cardiovascular, and neurodegenerative diseases, as well as other illnesses.<sup>1-7</sup> Many nanomedicines and nanodiagnostics are already FDA-approved and on the market, and many more are in clinical trials.<sup>8,9</sup> Currently, the most active areas of nanomedical research and product development are in cancer treatments, imaging contrast agents, and biomarker detection.<sup>8,10,11</sup> Although many nanotherapeutics and nanodiagnostics are already in use, there are many barriers that impede bringing nanomedical products to market.<sup>10-12</sup> However, despite these challenges, both large and small stakeholders are expected to continue to pursue research and investment in nanomedical applications, especially if they have novel properties, fulfill unmet medical needs, and offer a favorable cost-benefit outlook.<sup>12</sup>

### Clinical Applications for Nanomedicines

Nanomedicine is a rapidly growing area of medical research that is focused on developing NPs for prophylactic, diagnostic, and therapeutic applications.<sup>1</sup> Nanomedicines function on the same scale as many biological processes, cellular mechanisms, and organic molecules, so they are thought to provide an especially promising approach.<sup>11</sup> Methods and protocols for the synthesis, functionalization, and use of NPs have proliferated, presenting new strategies for molecular targeting, personalized therapies, and minimally invasive diagnostic techniques.<sup>11</sup>

Nanotherapeutics have already been FDA-approved and are available for clinical use, including treatments for cancer, high cholesterol, autoimmune disease, fungal infections, macular degeneration, hepatitis, and many other conditions (Table 1).<sup>1</sup> Additional medical applications for NPs include use in vaccinations, magnetic resonance imaging (MRI) contrast agents, fluorescent biological labels, pathogen detection, protein identification, DNA structure probing, tissue engineering, drug- and gene-delivery agents, and the separation of biological molecules and cells.<sup>1</sup> A review of nanomedical research applications, as well as FDA-approved drugs, devices, and diagnostics that utilize nanomedicine, follows.

### Cancer

Currently, cancer diagnosis and treatment rely primarily on invasive diagnostic techniques like biopsies and surgery and nontargeted treatments such as irradiation and chemotherapy.<sup>2</sup> Conventional nontargeted chemotherapy drugs lack specificity and therefore can cause significant damage to healthy tissues, resulting in undesirable side effects, such as bone marrow suppression, hair loss, and the sloughing of gut epithelial cells.<sup>2</sup> The diagnosis of early-stage cancer is also a significant challenge, because clinical symptoms don't always appear in time to prevent the disease from spreading to an advanced stage.<sup>2</sup> Therefore, earlier cancer diagnosis by minimally invasive means and targeted cancer treatments is urgently needed.<sup>2</sup> NP-based diagnostics and therapeutics offer more sensitive imaging strategies that result in earlier detection and targeted, tumor-specific agents that provide effective, noninvasive treatment.<sup>2</sup>

To that end, in order to improve the ability to diagnose various cancers, many highly specific and highly sensitive NP-based optical imaging platforms are currently being studied.<sup>2</sup> A major advantage that NP-based diagnostics offer, compared with other agents, is that they can be functionalized to specifically target tumor cells, allowing the imaging and therapeutic agents to be delivered directly to those cells.<sup>3</sup> These multifunctional NP complexes have optical, magnetic, and structural properties that single molecules do not have.<sup>13</sup> Strategies for constructing multifunctional NP complexes for cancer imaging and treatment involve: (1) encapsulation and/or (2) covalent or noncovalent binding of components that allow the NPs to recognize or locate the cancer; permit imaging of the tumor; deliver a therapeutic "payload;" and kill the tumor cells.<sup>3</sup>

Tumor-specific targeting is achieved by binding or conjugating the surface of NPs with a molecule or biomarker that attaches to tumor cell receptors.<sup>3</sup> The design of multifunctional NP complexes therefore requires knowledge of tumor-specific receptors, biomarkers, homing proteins, and enzymes that can permit selective cellular uptake of a diagnostic or therapeutic agent and subsequent accumulation in the tumor microenvironment.<sup>3</sup> Molecules and biomarkers that are commonly used for tumor targeting and conjugation include peptides, proteins, nucleic acids, and small-molecule ligands.<sup>3</sup> Synergistic effects could also be achieved by conjugating the multifunctional NP complex with different peptides and by loading it with multidrug regimens.<sup>3</sup> Complicated treatment regimens can also be devised through the use of heat-labile or protease-susceptible linkers that are degraded by the tumor microenvironment, allowing targeted drug release.<sup>3</sup> Such multifunctional NP complexes show tremendous promise for noninvasive tumor imaging and diagnosis.<sup>13</sup>

The discovery of the "enhanced permeation and retention (EPR) effect" also contributes to the success of NPs in targeting solid-tumor tissues, depending on size and other characteris-

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tics.<sup>4</sup> The EPR effect is the selective accumulation and retention of an agent in solid tumor tissue for a prolonged time. This effect is due to the discontinuous epithelium and disorganization of the tumor vasculature, increased leakiness of tumor

blood vessels, and decreased lymphatic drainage.<sup>4</sup> Because of the EPR effect, NPs are retained within the tumor tissue for a prolonged period because of the lack of adequate lymphatic clearance to remove them from the tumor.<sup>4</sup>

**Table 1 Examples of FDA-Approved Agents Utilizing Nanomedicine**

Trade Name	Active Ingredient	Indication*	Manufacturer	Approval
Abelcet	Liposomal amphotericin B	Invasive fungal infections	Sigma Tau	1995
Abraxane	Albumin protein-bound paclitaxel	Metastatic breast cancer	Celgene	2005
Adagen	Pegylated adenosine deaminase enzyme	Severe combined immunodeficiency disease	Sigma Tau	1990
Alimta	Pemetrexed	Nonsquamous NSCLC, malignant pleural mesothelioma	Lilly	2004
AmBisome	Liposomal amphotericin B	Fungal infections, leishmaniasis	Astellas/Gilead	1997
Amphotec	Liposomal amphotericin B	Invasive aspergillosis	Alkopharma	1996
Cimzia	Pegylated Fab' fragment of a humanized anti-TNF-alpha antibody	Crohn's disease, rheumatoid arthritis	UCB	2008
Copaxone	Glatiramer acetate (copolymer composed of L-glutamic acid, L-alanine, L-lysine, and L-tyrosine)	Multiple sclerosis	Teva	1996
DaunoXome	Liposomal daunorubicin citrate	HIV-associated Kaposi's sarcoma	Galen	1996
Depocyt(e)	Liposomal cytosine arabinoside	Lymphomatous meningitis	Pacira	1999
Doxil	Pegylated-stabilized liposomal doxorubicin	AIDS-related Kaposi's sarcoma, refractory ovarian cancer, multiple myeloma	Janssen	1995
Eligard	Leuprolide acetate and PLGH polymer formulation	Advanced prostate cancer	Sanofi	2002
Emend	Aprepitant nanocrystal particles	Chemotherapy-related nausea and vomiting	Merck	2003
Macugen	Pegaptanib (PEG-anti-VEGF aptamer)	Wet age-related macular degeneration	Eyetech	2004
Mircera	Methoxy PEG-epoetin beta	Symptomatic anemia associated with CKD	Hoffman La Roche	2007
Neulasta	Pegfilgrastim	Chemotherapy-associated neutropenia	Amgen	2002
Oncaspar	PEG-asparaginase	Acute lymphocytic leukemia	Sigma Tau	1994
Ontak	Interleukin-2 diphtheria toxin fusion protein	Cutaneous T-cell lymphoma	Eisai	1999
Pegasys	Peginterferon alpha-2a	Hepatitis B and C	Genentech	2002
PegIntron	Peginterferon alfa-2b	Hepatitis C	Merck	2001
Renagel	Amine-loaded polymer	Serum phosphorus control in patients with CKD on dialysis	Genzyme	2000
Somavert	Pegylated human growth hormone receptor antagonist	Acromegaly	Pfizer	2003
Tricor	Fenofibrate	Hypercholesterolemia, mixed dyslipidemia, hypertriglyceridemia	Abbott	2004
Visudyne	Liposomal verteporfin	Wet age-related macular degeneration, pathological myopia, ocular histoplasmosis syndrome	QLT Ophthalmics	2000

CKD = chronic kidney disease; NSCLC = non-small-cell lung cancer; PEG = polyethylene glycol; PLGH = poly (DL-lactide-co-glycolide); TNF = tumor necrosis factor; VEGF = vascular endothelial growth factor.

\* See official Product Information for more details regarding indications.

From References 2, 4, 7, 9, 10, 12, 17, and 30.

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However, only NPs within a specific size range can diffuse through the endothelium of tumor tissues and exploit the EPR effect.<sup>4</sup> The specific size of tumor vasculature defects depends on the cancer type, tumor site, and disease stage, but the upper size range of the gaps is generally around 300 to 400 nanometers (nm).<sup>4</sup> NPs must also be larger than 10 nm to avoid first-pass elimination in the kidney but smaller than 150 to 200 nm to avoid being cleared by the liver and spleen.<sup>4</sup> Therefore, NPs that range in size between 20 and 100 nm are essential for exploiting the EPR effect.<sup>4</sup> Fortunately, the sizes of many NPs fall within this desired range and can be further customized through “tuning.”<sup>4</sup> Tunable size properties, functionalization, and an ability to exploit the EPR effect are among the most significant reasons that NPs have become essential in the further development and improvement of cancer therapeutics.<sup>4</sup>

NP-based drug delivery can also improve the bioavailability and toxicity profile of cancer treatments. The majority of anticancer therapeutics are water-insoluble and therefore must be dissolved in an organic solvent prior to administration as an injectable solution.<sup>2</sup> These organic solvents are toxic and often have side effects.<sup>2</sup> The low molecular weight of many anticancer drugs also results in rapid excretion and a poor therapeutic index, requiring the administration of escalating doses, which increases cytotoxicity and other adverse events.<sup>2</sup> Nanoformulations of these chemotherapy agents could eliminate the need for organic solvents, increase bioavailability and retention time, improve the therapeutic index, decrease the need for dose escalation, and reduce adverse cytotoxic effects.<sup>2</sup>

### Cardiovascular Disease

Nanomedicine can also address challenges encountered in the treatment of cardiovascular disease (CVD). Potential benefits offered by nanomedicine include earlier diagnosis by *ex vivo* and *in vivo* biomarker detection and imaging, as well as improved therapy through targeted drug delivery or tissue regeneration.<sup>5</sup> One major focus of nanomedical applications for CVD has been the targeted imaging of atherosclerosis, restenosis, and other cardiovascular conditions.<sup>5</sup> Targets for the detection and imaging of atherosclerotic plaque include fibrin, tissue factor, endothelia, macrophages, collagen III, and angiogenesis markers.<sup>5</sup> In particular, fibrin deposition is one of the earliest signs of plaque rupture, so this, as well as tissue factor, are potential targets for sensitive NP-based ultrasound and MRI contrast agents.<sup>5</sup>

With traditional CVD therapies, it is also difficult to achieve sufficiently high drug concentrations at target sites without the possibility of causing serious side effects in healthy tissues.<sup>7</sup> Therefore, efforts in the past have been directed toward achieving targeted delivery to injured blood vessels by using drug-eluting stents.<sup>7</sup> The placement of these stents can reduce restenosis and target-vessel revascularization by more than 70% compared with bare-metal stents.<sup>6</sup> However, the polymer coatings and other features of drug-eluting stents may also result in increased thrombogenicity compared with bare-metal stents.<sup>6</sup> The vessel trauma that occurs during percutaneous coronary intervention also induces platelet activation.<sup>6</sup>

Because of these problems, nanomedical research in CVD has focused on using NPs for the targeted delivery of drugs that

treat atherosclerosis and restenosis, eliminating the need for drug-eluting stents.<sup>7</sup> Research has shown that the use of multifunctional NP complexes, conjugated with cell-specific ligands, makes it possible to deliver therapies directly to plaque cells.<sup>2</sup> Among the therapies that can be incorporated into a targeted NP complex to prevent atherosclerosis and/or restenosis are:<sup>5</sup>

- cytotoxic agents that inhibit smooth-muscle cell growth: paclitaxel, cytarabine, etoposide, and doxorubicin.
- platelet-derived growth factor (PDGF) receptor antagonists (tyrphostins).
- immunomodulators: steroids, bisphosphonates, Cyclosporine A.
- antibiotics (fumagillin).

Other promising nanotherapeutics for CVD focus on specific gene targets that are responsible for thrombosis or intimal hyperplasia (prostacyclin synthase and thymidine kinase).<sup>5</sup> These therapies can carry genes or other biomolecules that are encapsulated to provide protection against enzymatic degradation and to achieve a prolonged release profile.<sup>5</sup>

### Neurological Disease

Nanomedicine may also provide a solution for one of the greatest challenges that has ever faced the pharmaceutical industry—drug delivery across the blood–brain barrier (BBB).<sup>1</sup> The BBB is a tightly packed layer of endothelial cells that surrounds the brain and keeps high-molecular-weight molecules from entering.<sup>12</sup> Only a small number of drugs or small molecules with high-lipid solubility and a low molecular mass (less than 400 to 500 Daltons) can penetrate the BBB.<sup>12</sup> More than 98% of conventional medications exceed this size and molecular weight and are therefore unable to penetrate this barrier.<sup>1,12</sup> Consequently in 2010, the market occupied by the relatively small number of central nervous system (CNS) drugs that are available was less than one-fifth that of CVD drugs.<sup>1</sup>

Due to their small size and molecular weight, the ability of NPs to cross the BBB provides an important therapeutic advantage.<sup>1,14</sup> In fact, it has been found that NPs can be delivered directly to the brain without any functionalization or modification.<sup>12</sup> However, the pharmacological efficacy of a drug also depends on drug uptake and total drug exposure in the brain or CNS.<sup>1</sup> This, in turn, depends on a combination of factors besides the physical barrier presented by the BBB and the blood cerebrospinal fluid (BCSF). One of these factors is the affinity of the nanocarrier substrates for specific transport molecules located on both sides of the BBB.<sup>1</sup> These transport molecules, including growth factors, insulin, and transferrin, can increase the efficiency and kinetics of brain-targeted nanotherapeutics.<sup>1</sup>

The delivery of nanomedicines through the BBB and the BCSF also requires detailed knowledge of the range of possible routes to and from the CNS, proper functionalization (when required), and a means of verifying whether the nanocarrier has reached its final destination.<sup>12</sup> BBB permeability of drugs can be greatly increased through active targeting.<sup>1</sup> Nanocarriers, conjugated with ligands that attach to brain endothelial cell receptors, accumulate there and are eventually internalized by cells on the vascular side of the brain through the mechanism of receptor-mediated endocytosis.<sup>12</sup> These nanocarriers, which

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can also be conjugated with ligands that recognize brain tumor cells, have emerged as a major breakthrough in CNS drug delivery, especially in neuro-oncology.<sup>1</sup>

Nanomaterial research is also expected to develop novel, systemically administered diagnostic and therapeutic nanoprobes for the early diagnosis and treatment of a variety of intractable or age-related brain disorders, such as epilepsy, dementia, stroke, and Alzheimer's disease.<sup>1</sup> Nanoparticles engineered with antimicrobial features may also be able to cross the BBB, providing an effective treatment for brain infections, including meningitis.<sup>15</sup>

### Medical Devices and Diagnostics

#### Emerging Applications for Nanomaterials in Medical Devices

There are a wide range of potential applications for nanomaterials in medical devices.<sup>7</sup> For example, researchers are currently investigating the use of NPs in biocaptors, ocular implants, and artificial retinas.<sup>13</sup> Other potential medical device applications include neuroprostheses to replace damaged neurons, as well as cerebral implants designed to treat pain, depression, muscle damage, and neurodegenerative illnesses.<sup>9,13</sup>

Nanomaterials can be used alone, incorporated onto surfaces or into composites, or used as components of medical devices.<sup>15</sup> Mechanical stents with nanoscale components are also currently being researched for the treatment of CVD.<sup>5</sup> Stents incorporating nanomaterials use nanoporous substrates for targeted drug delivery and nanotextured surfaces to enhance biocompatibility.<sup>5</sup> Nanotexturing is also being investigated as a means of enhancing endothelial cell interaction with stent surfaces in order to eliminate the problem of impaired vessel revascularization that can occur after stent placement.<sup>5</sup>

An additional expected advancement is the integration of nanoporous stent surfaces with nanotextured features to enable the controlled time-release of antiproliferative agents to promote vessel endothelialization.<sup>5</sup> These features are expected to lower the incidence of restenosis and the occurrence of late-stage mortality attributed to thrombosis.<sup>6</sup> Nanoporous medical device platforms have also been investigated for the local delivery of cancer treatments.<sup>5</sup> Investigators have explored the utility of various nanoporous stent surfaces to deliver cancer drugs, including aluminum oxide for tacrolimus, carbon-carbon NP matrixes for paclitaxel, and gold or titanium oxide for other cancer therapies.<sup>5</sup>

Nanomaterial coatings for medical devices also provide a new approach against biofilm-mediated, drug-resistant, device-centered infections.<sup>15</sup> NPs with antibacterial properties, including zinc oxide, iron oxide, gold, and carbon nanotubes, are currently being developed for use in medical devices.<sup>15</sup> Such products that utilize the antibacterial properties of silver NPs have already been approved and are on the market.<sup>7</sup> Medical devices that incorporate carbon nanotubes into sensors that detect bacteria and release antibiotics only when needed are also being designed.<sup>15</sup>

Because some NPs mimic the constituent properties of natural tissues, nanomaterials are also being investigated as a promising tool for regenerative medicine and tissue engineering.<sup>15</sup> It is believed that implanted devices that include NP substrates or nanotextured surfaces enhance surface energy and selected protein adsorption, promote protein bioactivity, and improve tissue-forming cell functions.<sup>15</sup> In regenerative

medicine research, NP-coated or textured surfaces are therefore thought to be able to control tissue formation through promoting, and possibly directing, cell interactions.<sup>7</sup> Among other applications, the incorporation of nanomaterials in scaffolding used to promote nerve regeneration is currently being investigated.<sup>16</sup>

#### Emerging Applications for Nanomaterials in Medical Diagnostics

The use of NPs for biomarker detection and diagnostic imaging is considered one of the most significant and promising nanomedical applications in medicine. These important topics are discussed in more detail in the following section.

##### Biomarker Detection

Because NPs have unique chemical and physical properties, they can be used to improve the measurement of biomarkers and other molecules of interest in biological samples.<sup>5,17</sup> In fact, nanodiagnostic devices are expected to eventually supplant diagnostic tools that aren't as sensitive, convenient, efficient, or cost-effective, such as glucose test strips, chromatography, mass spectroscopy, and enzyme-linked immunosorbent assays (ELISA).<sup>18</sup>

Biomarker identification provides a powerful early, rapid, specific, minimally invasive, low-cost approach to screening, diagnosis, prognosis, and therapeutic monitoring.<sup>5,10</sup> Because of these advantages, the development of biosensors that incorporate nanomaterials for biomarker detection has become an area of intense research.<sup>18</sup> In fact, some biomarker detection devices have already undergone technological improvements, such as a lower limit of detection and improved efficiency, through the inclusion of nanomaterials.<sup>5,10,17</sup> These advances provide access to biomarkers expressed at low concentrations, not only in plasma but also in serum, saliva, tears, and other fluids that contain potentially relevant analytes.<sup>10</sup>

Tunable nanoporous materials have also been used to selectively harvest low-molecular-weight proteins, providing a unique opportunity to detect and identify new circulating biomarkers after fractionation of body fluids.<sup>5</sup> Nanowires also offer great diagnostic potential through the ability to measure pH variations or detect trace amounts of biological and chemical substances.<sup>5</sup> In addition, nanobiochips are versatile molecular diagnostic tools that can improve the accuracy and sensitivity of biomarker detection by orders of magnitude.<sup>5,19</sup> They are important components of "labs-on-a-chip," which are expected to have an especially significant impact on the development of point-of-care diagnostics.<sup>19</sup>

The ability of nanodiagnostic devices to detect low levels of biomarkers is also expected to be significant in other ways. Clinical trials and research efforts have indicated that continuous metabolic monitoring holds great potential to provide early detection of various diseases and disorders.<sup>18</sup> Currently, cancer diagnosis relies mainly on protein quantification or the detection of a tumor mass a few cubic millimeters (mm) or more in size that already contains millions of cancer cells.<sup>10</sup> There is mounting evidence that for some cancers, metastasis may occur earlier than previously thought, so waiting until a detectable tumor develops can present a higher risk to the patient's health.<sup>10</sup> The possibility that nano-enabled diagnostic devices may be able to detect low levels of important cancer biomarkers, such as circulating tumor DNA, messenger RNA



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(mRNA) transcripts, polysomes, micro-RNA (miRNA), proteins, metabolites, and autoantibodies, may provide the needed assistance for this disease to be detected at an earlier stage.<sup>10</sup>

Earlier detection of CVD will also permit the more timely intervention and management of this disease.<sup>5</sup> The prognosis for patients with CVD can also be improved through more sensitive, specific, and rapid assessment of diagnostic markers. Biomarkers that can better distinguish high-risk populations for CVD have already been identified, including C-reactive protein, B-type natriuretic peptide, fibrinogen, D-dimer, and homocysteine.<sup>5</sup> Faster, more sensitive, cost-effective biomarker-detection devices could also potentially provide an early signal of metabolic imbalances that develop into various disorders, like diabetes and obesity.<sup>18</sup>

Device miniaturization, which explores the use of implantable biochips and biosensors for medical diagnostics, is another important application that utilizes nanomaterials.<sup>9</sup> An implantable device needs to be extremely small, requiring unprecedented miniaturization of components such as electrodes, power sources, signal-processing units, and sensory elements.<sup>18</sup> The nanoscale dimensions, electrocatalytic properties, and high surface area of single-walled and multiwalled carbon nanotubes have prompted researchers to utilize these NPs as nanoelectrodes.<sup>18</sup> Micro- and nano-fabrication involving traditional semiconductor processes, such as photolithography, wet and dry etching processes, dip-pen nanolithography, and micromachining, provide an additional path to sensor miniaturization.<sup>18</sup>

Miniaturized, implantable biosensors may provide the ability to continuously measure metabolite levels without the need for patient or clinician intervention.<sup>18</sup> Nanochips and nanosensors can be integrated in existing implants such as defibrillators, stents, and pacemakers in order to trigger a warning, transmit data, and/or activate drug release.<sup>5</sup> They may also permit clinicians to access and examine patients remotely.<sup>9</sup> Other applications for implantable biosensors could involve internal and intracellular evaluation, such as DNA analysis.<sup>9</sup> Another interesting avenue of research is the incorporation of imaging capability in implantable devices through the use of fluorescent NPs.<sup>18</sup> These imaging agents could track performance and device degradation and also assist in monitoring leached nanomaterials.<sup>18</sup> Another effort being investigated is the engineering of implantable nanodevices that can be triggered to biodegrade when no longer needed, similar to biodegradable sutures used for surgery.<sup>18</sup>

### Biomedical Imaging

Traditional clinical imaging modalities are associated with high costs, low sensitivity, and/or low spatial resolution, prompting a search for more sensitive and specific imaging techniques.<sup>1</sup> Contrast agents containing NPs are emerging as useful tools that fulfill this need.<sup>5</sup>

Because of their optical and magnetic properties, metallic NPs, such as paramagnetic iron oxide (IO) or superparamagnetic iron oxide NPs (SPIOs), have the potential to profoundly alter existing clinical diagnostic and therapeutic methods.<sup>2,3</sup> Magnetic NPs used in biomedical applications usually consist of an inorganic NP core and a surface coating that facilitates targeting and/or confers stability in aqueous dispersions.<sup>2</sup> The use of contrast agents containing SPIOs, compared with conventional MRI imaging agents, has been found to substantially increase both diagnostic sensitivity (90.5% vs.

35.4%) and specificity (97.9% vs. 90.4%) in the detection of metastatic tumors.<sup>17</sup> In addition, ferumoxtran-10 and its derivative, ferumoxytol, are examples of ultra-small SPIOs (USPIOs) that have been shown to improve MRI of tumors in animal models.<sup>2</sup> Other NPs being investigated for use in diagnostic imaging include fluorescent and radioactive as well as electron-dense and light-scattering NPs.<sup>5</sup> Imaging methods using fluorescent NPs have especially unique advantages in that they are simple and economical, requiring smaller-sized equipment.<sup>1</sup>

Unlike conventional contrast media, NP-based imaging agents can be designed to be targeted, multicomponent, multitasking, and multimodal, allowing the simultaneous detection and treatment of disease.<sup>5</sup> Multifunctional NP complexes that integrate imaging and therapeutic components are referred to as “theranostic” agents.<sup>5</sup> These next-generation MRI contrast agents consist of various nanosized core materials, such as SPIO NPs, that are attached to tumor-specific conjugates for improved tumor targeting and therapeutic capabilities.<sup>2</sup> Theranostic NPs can deliver dosage regimens and verify, monitor, and quantify the effect on the intended site of action to determine treatment outcome.<sup>5</sup> Drug delivery via multifunctional NPs and multimodal imaging could, in principle, simultaneously treat and monitor the status of a tumor, thus increasing the patient’s likelihood of survival.<sup>1</sup> Although the development of theranostics is still in its infancy, this strategy has numerous potential advantages, which are being extensively investigated in cancer treatment.<sup>5</sup>

Computed tomography (CT) represents another diagnostic imaging application in which NPs have been shown to enhance imaging contrast.<sup>5</sup> An interesting set of studies explored the use of nanoliposomes as carriers for contrast agents used in CT, such as iodine.<sup>5</sup> In animal models, these systems were shown to efficiently prevent a rapid clearance of the contrast agent from the body, thereby significantly improving total blood pool and cardiac imaging capability.<sup>5</sup>

The ability to image cellular migration *in vivo* could also be very useful for studying inflammation, tumors, immune response, and effects of stem-cell therapy.<sup>3</sup> As promising cellular treatments move forward, there is a critical need for noninvasive, objective methods that identify and track cells once they have been transplanted.<sup>3</sup> NPs provide an excellent solution for this, since they have been successfully used in experimental studies to label and track transplanted human mesenchymal and neural stem cells, as well as hematopoietic, Schwann, olfactory ensheathing, and oligodendrocyte precursor cells, among others.<sup>3,13</sup>

### Examples of FDA-Approved Drugs, Devices, and Diagnostics Utilizing Nanomaterials

#### Drugs for Cancer Treatments

Cancer treatments represent the largest therapeutic area for approved nanomedicines, as well as for patents and research publications.<sup>11</sup> Thanks to new treatment strategies, patients are now benefiting from new chemotherapy drugs that utilize nanocarriers to lower systemic toxicity and improve therapeutic efficacy.<sup>11</sup> The increasing acceptance of nanomedicines, along with the desire to use all available means to control aggressive cancers, has also been a strong driver for the advances in this segment.<sup>11</sup> Doxil (liposomal doxorubicin HCl injection,

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Janssen) and Abraxane (paclitaxel protein-bound particles for injectable suspension, Celgene) are two notable examples of FDA-approved cancer nanomedicines that have been clinically successful.<sup>11</sup>

### Doxil

In 1995, Doxil, a circulating sustained-release liposomal nanoformulation of doxorubicin, became one of the first nanomedicines approved by the FDA.<sup>2</sup> It was first approved for the treatment of AIDS-related Kaposi's sarcoma and later for refractory ovarian cancer and multiple myeloma.<sup>11</sup> Conventional doxorubicin is a chemotherapeutic agent that is widely used in the treatment of breast, ovarian, bladder, and lung cancer. It is very effective, but severe side effects, such as cardiotoxicity and myelosuppression, have limited its use.<sup>2,10</sup>

Doxil has demonstrated significantly improved safety and efficacy compared with conventional doxorubicin.<sup>2</sup> The current Doxil formulation contains doxorubicin in polyethylene glycol (PEG)-coated liposomes that are about 100 nm in diameter.<sup>10</sup> The liposomal formulation reduces the cardiotoxicity of doxorubicin, since it reduces the peak cardiac level of the drug. Clinical study results also suggest that encapsulation of doxorubicin in liposomal NPs improves the therapeutic efficacy of Doxil due to extended circulation time and accumulation at tumor sites through exploitation of the EPR effect.<sup>2</sup>

### Abraxane

In early 2005, Abraxane, an albumin-bound nanoformulation of paclitaxel, was approved for the treatment of refractory metastatic breast cancer.<sup>2,3,11</sup> Conventional paclitaxel (Taxol) is poorly soluble in aqueous solutions, so its formulation includes Cremophor EL (polyethoxylated castor oil, BASF) and ethanol.<sup>10</sup> However, Cremophor EL is cytotoxic and induces side effects; therefore, a new paclitaxel formulation was sought.<sup>9</sup>

The nanoformulation of Abraxane includes a 130-nm albumin-bound NP form of paclitaxel.<sup>10,20</sup> Albumin is the human body's key transporter of water-insoluble molecules, such as various nutrients, vitamins, and hormones, so the Abraxane formulation does not require the use of other excipients.<sup>10,20</sup> Abraxane does not contain Cremophor EL, so premedication with steroids or antihistamines, used to manage hypersensitivity reactions caused by the solvent, is not needed.<sup>3</sup> Abraxane also takes 30 minutes to administer, whereas Taxol takes up to 3 hours.<sup>20</sup>

The nanoformulation of Abraxane targets tumors through the EPR effect, specifically by binding to the endothelial glycoprotein 60 (gp60) receptor and albumin binding proteins that are overexpressed in many tumors.<sup>10</sup> In a randomized, multicenter trial that enrolled 460 subjects, patients receiving Abraxane had a statistically significant higher target lesion response rate (21.5% vs 11.1%;  $P = 0.003$ ) compared with those receiving the conventional paclitaxel formulation.<sup>3</sup> Patients treated with Abraxane also had less intense side effects even though a higher dose of conventional paclitaxel had been administered.<sup>3</sup> Currently, Abraxane is being evaluated for numerous other cancers, including melanoma, as well as cervical, peritoneal, ovarian, and non-small-cell lung cancers.<sup>12,21</sup> Other paclitaxel nanoformulations are also being developed, including a polymeric micelle formulation (Genexol-PM, Samyang) that also eliminates the need to use Cremophor EL as a solubilizer.<sup>10,17</sup>

### Other Types of Nanomedicines

Although the most active area of nanomedical research and drug approvals has been in oncology, nanotherapeutic agents for the treatment of other diseases are also available.

Several FDA-approved nanoformulations of liposomal amphotericin B are available for the treatment of severe fungal infections; they are Abelcet (Sigma Tau), AmBisome (Astellas/Gilead), and Amphotec (Alkopharma).<sup>21</sup> These drugs were approved by the FDA in 1995, 1997, and 1996, respectively (see Table 1, page 583). Liposomal formulations of amphotericin B have been shown to be more effective and safer than conventional amphotericin B formulations.<sup>11</sup>

Emend (aprepitant, Merck) is an antiemetic drug for patients who are receiving chemotherapy or have undergone surgery.<sup>16</sup> It contains 40, 80, or 125 mg of aprepitant formulated as NanoCrystal (Elan) drug particles.<sup>16</sup> NanoCrystal particles are NPs of a drug substance, typically less than 1,000 nm in diameter, that are produced using a proprietary, wet-milling technique.<sup>16</sup> Emend was approved by the FDA in 2003.<sup>16</sup> Compared with earlier conventional aprepitant formulations, Emend has superior bioavailability and a reduced food effect.<sup>20</sup>

TriCor (fenofibrate, Abbott) is indicated for hypercholesterolemia, mixed dyslipidemia, and hypertriglyceridemia.<sup>16</sup> TriCor also uses NanoCrystal technology and was reformulated in 2004, replacing the previous conventional fenofibrate formulation.<sup>16</sup> Reduced doses of nanoformulated Tricor are as safe and effective as higher doses of the previous conventional formulation.<sup>16</sup> The nanoformulation of TriCor also eliminated the requirement that the tablets be taken with a meal.<sup>16</sup>

### Medical Devices

Many types of nanomaterials are currently being investigated for various applications that will improve medical devices. A couple of examples follow. A partial listing of medical devices, imaging agents, and diagnostics that incorporate nanomaterials is also provided in Table 2.

SilvaGard (AcryMed, Inc.), FDA-approved in late 2005, is a silver NP antimicrobial surface treatment solution that deposits silver particles on the surface of medical devices after they are manufactured.<sup>20</sup> SilvaGard utilizes the antimicrobial properties of ionic silver to prevent infection-causing biofilms.<sup>20</sup>

Vitoss (Orthovita), FDA-approved in 2000, is a three-dimensional scaffold composed of ultraporous beta-tricalcium phosphate (TCP) NPs (mean size, 100 nm). The nanosized beta-TCP particles, which enhance resorption and new bone growth, are used in repairing bone defects. Many variations of Vitoss products have been introduced to the market by Orthovita since 2000.<sup>22</sup>

### Imaging Agents

Nanoformulated imaging agents contain NPs of iron oxide; gadolinium derivatives; or bioessential manganese, cobalt, nickel, or copper ions.<sup>23</sup> Some of these agents have been FDA-approved for clinical use, but many more are still under development.<sup>23</sup>

The majority of MRI contrast agents currently available in clinics are small-molecule gadolinium chelates.<sup>23</sup> One of the first successful applications of NPs in the clinic was the gadolinium-based injectable paramagnetic contrast agent Omniscan (gadodiamide, General Electric Healthcare), which was FDA-

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approved in 1993.<sup>11</sup> This contrast agent has been utilized ever since, in both cardiology and neurology, to detect strokes and brain tumors.<sup>11</sup> Another injectable gadolinium-based contrast agent is Optimark (gadoversetamide, Mallinckrodt), which was FDA-approved in 1999.<sup>11</sup> It allows the visualization of lesions with atypical vascularity and is used for MRI scans of the brain, liver, and spine.<sup>11</sup> Finally, MultiHance (gadobenate dimeglumine, Bracco Group) is an extracellular fluid contrast agent that was FDA-approved in 2004.<sup>11</sup> It interacts with plasma proteins and is used in MRI scans of blood vessels, organs, and the CNS.<sup>11</sup>

Iron oxide NPs used in MRI scans are usually divided into two size categories: standard SPIOs or IOs (larger than 50 nm) and USPIOs (smaller than 50 nm).<sup>23</sup> Currently, FDA-approved SPIOs for imaging are limited to only a few formulations—Gastromark (silicone-coated ferumoxsil SPIOs, AMAG/Mallinckrodt), Abdoscan (polystyrene-coated ferristene SPIOs, Nycomed Imaging), and Feridex (dextran-coated ferumoxide SPIOs, AMAG).<sup>5</sup> Gastromark is currently used as a bowel-contrast agent, and Abdoscan and Feridex were used for spleen and liver imaging before these products were discontinued by the manufacturers in 2002 and 2008, respectively.<sup>2,23</sup>

Combidex (dextran-coated ferumoxtran-10), a USPIO, represents one of the major successes in this class of NPs.<sup>2</sup> It has been approved in some European countries but not in the U.S. Combidx is currently being investigated for the detection of brain and pancreatic cancer and lymph node metastases in clinical trials in the U.S.<sup>2,21</sup>

### Diagnostics

A number of diagnostic devices utilizing nanomaterials have been approved by the FDA. Several of them are described in the following section.

The CellSearch test (Veridex LLC/Johnson & Johnson) uses IO NP-bound antibodies to capture and quantify circulating breast, colorectal, or prostate tumor cells in blood samples.<sup>10</sup> This test first received FDA approval for the detection of metastatic breast cancer cells in 2004, then for colorectal and prostate cancer cell screening in 2007 and 2008, respectively.<sup>10</sup> CellSearch is often used during cancer clinical trials to detect circulating tumor cells (CTCs).<sup>10</sup>

CombiMatrix DNAarray tests are lab-on-a-chip devices for identifying and investigating genes, gene mutations, and proteins. These miniaturized, microfabricated, semiconductor biochip-based systems are capable of performing standard or customizable multiplexed assays involving DNA, RNA, proteins, peptides, or small molecules, so they have many potential applications. The first CombiMatrix Diagnostics product was introduced in 2005.<sup>16</sup>

Verigene (Nanosphere) diagnostic tests incorporate gold NPs that are modified with either a nucleotide sequence or antibodies.<sup>24</sup> These conjugates are customized to bind to a DNA sequence or protein in the target of interest. The gold NPs increase sensitivity by several orders of magnitude, enhance specificity, reduce background noise, are stable, have a long shelf life, and are nontoxic.<sup>24</sup> In 2007, Nanosphere received

**Table 2 Examples of Medical Devices and Diagnostics Utilizing Nanomedicine**

Name	Device/Diagnostic Type	Application	Manufacturer	Year Approved
<b>FDA-Approved</b>				
CellSearch	Antibodies bound to IO NPs	CTC detection	Veridex	2004
DNAarray	Lab-on-a-chip	DNA-based tests	CombiMatrix	2005
Gastromark	Silicone-coated ferumoxsil SPIOs	MRI contrast agent	AMAG Pharmaceuticals	1996
MultiHance	Gadolinium-based NPs	MRI contrast agent	Bracco Group	2004
Optimark	Gadolinium-based NPs	MRI contrast agent	Mallinckrodt	1999
Omniscan	Gadolinium-based NPs	MRI contrast agent	General Electric Healthcare	1993
Silvagard	Silver NP solution	Anti-infective coating for medical devices	AcryMed, Inc.	2005
Verigene	Functionalized gold NPs	Diagnostic tests	Nanosphere	2007
Vitoss	Ultraporous beta-TCP NPs	Bone-replacement scaffold	Orthovita	2000
<b>Investigational</b>				<b>Status (U.S.)</b>
Combidex	Dextran-coated ferumoxtran-10 USPIOs	MRI contrast agent	Advanced Magnetics	Phase 1, 2, 4
MagProbe	CD34 antibody-linked NPs/magnetic biopsy needle	Leukemia diagnosis	Senior Scientific	Phase 1
NanoTherm therapy	Aminosaline-coated IO NPs	Thermal ablation/hyperthermia therapy for liver, pancreatic cancer	MagForce AG	Preclinical
CTC = circulating tumor cell; IO = iron oxide; MRI = magnetic resonance imaging; NP = nanoparticle; SPIO = superparamagnetic iron oxide; TCP = tricalcium phosphate; USPIO = ultra-small superparamagnetic iron oxide. Data from References 9, 17, 21, and 22.				

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FDA approval for the Verigene pharmacogenetic test for warfarin metabolism.<sup>25</sup> Since then, other Verigene tests have been approved for the detection of the *F5*, *F2*, and *MTHFR* genes and the identification of respiratory viruses or gram-positive bacterial pathogens.<sup>25</sup>

### Current Clinical Trials Investigating Nanomedicines

Numerous medical applications for NPs are being investigated in clinical trials, and many more proof-of-concept studies in cell cultures or small-animal models are under way.<sup>17</sup> A search conducted at ClinicalTrials.gov, a database of federally and privately supported clinical trials in the U.S. and abroad, currently lists 111 clinical trials involving NPs.<sup>21</sup> An abbreviated listing of some NPs that are being investigated in clinical trials is provided in Table 3.

One notable cancer nanomedicine in clinical trials is BIND-014 (targeted polymeric NP complex containing docetaxel, Bind Biosciences).<sup>26</sup> BIND-014 is a multifunctional NP complex, consisting of a polymer matrix, therapeutic payload of docetaxel, functional surface conjugates, and targeting ligands. These components allow for accumulation in target tissue, avoidance of clearance by the immune system, and the desired release profile for the drug.<sup>26</sup> BIND-014 is unique in that it is the first multifunctional NP complex to be tested in a human clinical trial.<sup>27</sup> The phase 1 study, which began in January 2011, utilizes

an ascending, intravenous (IV) dose design to assess the safety, tolerability, and pharmacokinetics of BIND-014 in patients with solid tumors.<sup>26</sup> The primary objectives of the study are to determine the maximum tolerated dose of BIND-014 and to assess preliminary evidence of antitumor activity.<sup>26</sup> Preliminary data indicate that in a patient population (n = 17) with advanced or solid tumors, BIND-014 accumulates at tumor sites and displays clinical efficacy at doses as low as 20% of conventional docetaxel, even in cancers that are not usually affected by this drug.<sup>27</sup> BIND-014 was also found to be well tolerated, with no new toxicities observed to date in the human clinical trial.<sup>27</sup>

Another highly anticipated cancer nanomedicine is Aurimune (CytImmune Sciences) for the treatment of patients with advanced or metastatic cancers who are no longer responsive to conventional treatment.<sup>17</sup> Aurimune contains solid gold NPs, with a mean diameter of 30 nm, that have been functionalized with recombinant human tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ).<sup>10</sup> The surface of the colloidal gold NPs in Aurimune are pegylated so that the therapeutic payload can avoid immune detection and travel safely through the bloodstream.<sup>10</sup> Histopathology studies have shown that these NPs localize within or around the tumor, with less uptake by healthy organs than is seen with conventional TNF- $\alpha$ .<sup>17</sup> The therapeutic use of conventional formulations of cytokines such as TNF- $\alpha$  is limited by the inflammatory responses they produce, especially when

**Table 3 Examples of Investigational Agents Utilizing Nanomedicine**

Name	Active Ingredient	Condition	Manufacturer	Status in U.S.
L-Annamycin	Liposomal annamycin	Children and young adults with refractory or relapsed ALL or AML	Callisto Pharmaceuticals	Phase 1, 2
Aurimune	Recombinant human TNF conjugated to gold NPs	Solid tumors	Cytimmune Sciences	Phase 1
AuroShell	Gold-coated silica nanoshells	Head and neck cancer, solid tumors	Nanospectra Biosciences	Phase 1
BikDD NP	Liposomal pro-apoptotic <i>Bik</i> gene (BikDD)	Pancreatic cancer	MD Anderson Cancer Center/ National Cancer Institute	Phase 1
BIND-014	Targeted multifunctional polymeric NP complex containing docetaxel	Advanced or metastatic cancer, solid tumors	BIND Biosciences	Phase 1
CALAA-01	Anti-R2 siRNA/cyclodextran- containing polymer (CAL 101) and targeting agent (AD-PEG-Tf)	Solid tumors refractory to standard-of-care agents	Calando Pharmaceuticals	Phase 1
Docetaxel-PNP	Docetaxel polymeric NPs	Advanced solid malignancies	Samyang Biopharmaceuticals	Phase 1
Genexol-PM	Methoxy PEG–PLA paclitaxel	Breast and lung cancer	Samyang Biopharmaceuticals	Phase 2
Myocet	Liposomal doxorubicin	Metastatic breast cancer	Sopherion Therapeutics	Phase 3
Rexin-G	Dominant-negative cyclin G1 construct pathotropic NP	Recurrent or metastatic breast cancer, pancreatic cancer, sarcoma	Epeius Biotechnologies	Phase 1, 2
Arikace	Liposomal amikacin	Bronchiectasis, cystic fibrosis, bacterial lung infections	Insmed	Phase 1, 2

AD-PEG-Tf = adamantane–pegylated-transferrin; ALL = acute lymphocytic leukemia; AML = acute myelogenous leukemia; BiK = (Bcl-2 interacting killer); NHL = non-Hodgkin's lymphoma; NP = nanoparticle; PEG-PLA = polyethylene glycol-poly(lactic acid); siRNA = small inhibitory RNA; TNF = tumor necrosis factor.  
Data from References 2, 7, 10, 12, 17, and 21.



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tissues are exposed to high doses.<sup>17</sup> However, with IV injection of Aurimmune, patients have been able to tolerate 20 times the usual dose of conventional TNF- $\alpha$ .<sup>17</sup>

AuroShell (Nanospectra Biosciences) is currently being studied in clinical trials of patients with head and neck cancer.<sup>28</sup> AuroShell particles are optically tunable, with a mean diameter of 150 nm, and are composed of a silica core coated with an ultra-thin gold shell.<sup>18</sup> These particles are injected into patients intravenously and collect in tumors as a result of the EPR effect.<sup>12,29</sup> Following accumulation in tumors, the area is illuminated with a near-infrared laser at wavelengths that allow penetration through healthy tissues without harming them.<sup>29</sup> The metal in the AuroShell particles convert the absorbed light into heat with high efficiency, acting as heat generators for thermal ablation therapy, which destroys a tumor from within.<sup>29</sup> Theoretically, this technology could be useful for the eradication of all solid tumors, including breast, prostate, and lung cancers.<sup>12</sup> However, the toxicity of gold remains to be fully investigated.<sup>12</sup>

### Barriers to the Clinical Development Of Nanomedicines

Although many nanomedicines are already in use or are being studied in clinical trials, many barriers impede bringing these drugs to market.<sup>10</sup> Multiple challenges and risks make converting nanomedical research into commercially available medical products extremely complicated.<sup>12</sup>

One challenge is the FDA-approval process.<sup>12</sup> This complex and demanding process, as well as other FDA regulations, makes bringing nanomedicine products to market much more difficult than introducing other types of nanotechnology products that are not as stringently regulated.<sup>11,17</sup> Administrative burdens can delay the initiation of a clinical trial for an average of 800 days.<sup>10</sup> Patient enrollment can also be challenging, with as few as 3% of eligible patients participating in cancer clinical trials.<sup>10</sup> Compared with conventional medicines, relatively few clinical trials are investigating NPs (only 0.09% of the trials currently listed at Clinicaltrials.gov), so the potential of many nanomedicines is yet to be determined.<sup>10,17,21</sup> Because of these and other factors, nanomedical products currently occupy only a tiny niche of the total drug, biotech, and device market.<sup>12</sup>

Attracting investment for nanomedicine research is also particularly challenging.<sup>11</sup> Investment in nanomedical research is currently driven by small and medium-sized companies and venture capitalists who invest in startups.<sup>12</sup> Universities are also pushing for funding to adapt basic nanomedical research into real products.<sup>12</sup> However, investors are extremely cautious about making large investments in nanomedicine, because positive returns occur only over the long term, if at all.<sup>11</sup> Most, if not all, of these companies and university groups will eventually partner with large biotech or drug companies to make their enterprises a business success.<sup>12</sup> However, the fact that there have been relatively few commercially viable nanomedical products to date makes finding such a partner difficult.<sup>11</sup> Investors are also concerned about whether the FDA will be even more stringent in regulating nanomedicines in the future, even though these products are currently regulated like conventional drugs.<sup>12</sup> Multiple NP patent applications have also been filed at the U.S. Patent and Trademark Office, which has

granted surprisingly broad patents.<sup>12</sup> This has created confusion, because competing interests are unsure of the validity and enforceability of the patents.<sup>12</sup>

The process of bringing a medicine, device, or diagnostic to market is so complicated and expensive that pharma and biotech companies also tend to want to focus on drugs that are expected to be blockbusters.<sup>11</sup> However, potential blockbusters are difficult to identify, because of a scarcity of data.<sup>11</sup> It has therefore been suggested that stakeholders, including research scientists, clinical investigators, health care providers, patient associations, and investors, develop a shared communication platform to facilitate communication and collaboration.<sup>11</sup> An international, central “nanoparticle databank” could characterize NPs and summarize animal studies and clinical trial data.<sup>12</sup> This database could ultimately benefit patients, health care providers, and investors alike by helping to bring innovative and profitable medical products to market.<sup>11</sup>

Despite these problems, investments in nanomedicine are expected to increase.<sup>11</sup> Pharma and biotech companies are still expected to embrace nanotherapeutics and other nanomedical products, especially if they have novel properties, fulfill unmet medical needs, and offer an attractive cost-benefit ratio.<sup>12</sup> The success of nanomedicines like Doxil and Abraxane, and an expanding market for nanotherapeutics, has made the risk-reward ratio for these agents more appealing.<sup>11</sup> Illustratively, in 2009, venture capitalists doubled their investment in nanomedicine (in contrast to 2007), at the expense of the information technology market.<sup>11</sup> Presently, investment in nanomedicine dominates venture capital funding in the health care market, predicting a bright future for this promising area of research.<sup>11</sup> Nanomedicine is also expected to create additional revenue streams for pharmaceutical companies by creating new patentable formulations of off-patent proprietary drugs, extending the life of these products.<sup>12</sup> It is even expected that novel or reformulated nanotherapeutics will disrupt the generic drug market.<sup>12</sup>

### Conclusion

Nanomedicines have unique properties that can potentially provide novel solutions in the treatment of many diseases. A number of FDA-approved therapeutics, medical devices, imaging agents, and diagnostic devices containing nanomaterials have already become available, advancing medicine and improving health care.<sup>30</sup> Despite substantial barriers that impede the development and availability of nanomedical products, it is expected that research and investment in this area will continue at a rapid pace, causing these products to become an integral part of mainstream medicine in the future.

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